MULTI-DRUG TREATMENT STRATEGY FOR REFRACTORY CANINE BABESIOSIS: A CASE REPORT

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ABSTRACT

Present case report discuss with a case of refractory canine babesiosis in a 4 year male golden retriever and its multidrug treatment strategy. Dog came with clinical signs of anorexia and lethargy and history of two instances of treatment for babesiosis. Clinical examination reveals fever, tachycardia, pale mucous membrane and dehydration. The treatment of dog was continued with Clindamycin @25 mg/kg b.wt bid, Doxycycline @ 5mg/kg b. wt bid, Metronidazole @15 mg/kg b. wt bid and Pantaprazole once daily for six weeks. Dog recovered uneventfully and there is no history of relapse after 1.5 year

Key words: Babesiosis, refractory, canine, clindamycin, doxycycline, metronidazole

Introduction

Canine babesiosis is a tick-borne illness caused by a protozoon of the *Babesia* species with worldwide prevalence (Baneth, 2018). The incidence of canine babesiosis has been reported to be increasing in different regions of India, including the north-eastern area (Bhattacharjee and Sharma, 2013).Currently recognized *Babesia* species in canine have large form (*Babesia canis*, *Babesia vogeli, Babesia rossi*) and small form (*Babesia gibsoni, Babesia conradae, Babesia vulpe*) (Baneth, 2018).Most clinical signs found in canine babesiosis account for hemolytic anemia with erythrocyte destruction and systemic inflammatory response that may lead to organ dysfunction (Eichenberger *et al*., 2016; Augustine *et al*., 2017; Baneth, 2018). The definitive diagnosis is based on the demonstration of

Babesia spp. in red blood cells on Wright's or Giemsa's stain. In India,several drugs, including babesiacidal agents, (*e.g*., diminazene aceturate, imidocarb diproprionate) antiprotozoal (*e.g*., atovaquone) and antibiotics (*e.g*., clindamycin, doxycycline, azithromycin) have been used in canine babesiosis management (Joshi *et al*., 2017; Bhat *et al*., 2019; Hasan *et al*., 2019; Raghuvaran *et al*., 2019). None of these drugs can completely eliminate the *B. gibsoni.* So, there is a need to investigate the synergistic consequences of drug combinations against *B. gibsoni* infection.

This report describes the treatment and outcome of a combination of the clindamycin-doxycycline-metronidazole drug against refractory *B. gibsoni* infection in a dog that was diagnosed based on the history, clinical assessments, ultrasonography, and Giemsa-stained smear examination.

Case Presentation

A 4-year old male golden retriever, vaccinated client-owned dog was referred to the Veterinary Clinical Complex (VCC), Lakhimpur College of Veterinary Science, North Lakhimpur, Assam, India.

History and presenting sign

He had a history of anorexia, fever, and lethargy for the last three days and two instances of treatment for *B.gibsoni* infection. On the first occasion, the dog was treated with diminazene aceturate and recovered from the clinical sign within two weeks of treatment. After 18 days of initial treatment the dog relapsed. In the second instance, the dog was treated with a combination of diminazene aceturate and clindamycin. The dog recovered uneventfully after 14 days of treatment. However, the dog showed anorexia after two months.

Physical, laboratory and radiological evaluation

On admission, clinical examination revealed fever, tachycardia, pale mucous membrane, and dehydration. A complete blood count revealed anaemia haemoglobin [Hb]: 8.3 g/dl: reference range; 11.9 g/dl-18.9g/dl) (Kahn and Line, 2010), leukocytosis (white blood cell:23.8 x $10^3/\mu l$; reference range 5x10^3/micro litre-14.1x $10^3/\mu l$) (Kahn and Line, 2010).Whole abdominal ultrasonography revealed normal study for major abdominal organs like gall bladder (GB), liver, Kidney, urinary bladder (UB) with the absence of calculi in UB, and calculi. However, spleen appears to have mild increased in echogenicity, bipolar rounded appearance of spleen but with normal contour and parenchyma: hilum to periphery size was 2.43 cm. All these suggestive of nontumor splenomegaly (Fig 1). Giemsa staining of peripheral blood revealed *B. Gibsoni* organisms (Fig 2). Based on this observation; it was confirmed to be the relapse of *B. gibsoni* infection.

Diagnosis

Based on these observations it was confirmed to be a relapse of *B.gibsoni* infection (Paltrineri, 2017)

Treatment and outcome

Based on the literature on the drug-resistant strains of *Babesia gibsoni*, therapeutic medication was then changed to combination therapy with clindamycin tablet (Bioclan®, SavaVet, India; 25 mg/kg b.wt., orally, bid), doxycycline tablet (Doxy Pet®, Sava Vet, India; 5 mg/kg b.wt., orally, bid), Metronidazole tablet (Metron Forte®, Indemic, India, 15 mg/kg

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Fig.1: Represents normal spleen contour and parenchyma but with increased hilum periphery size (2.45 cm)

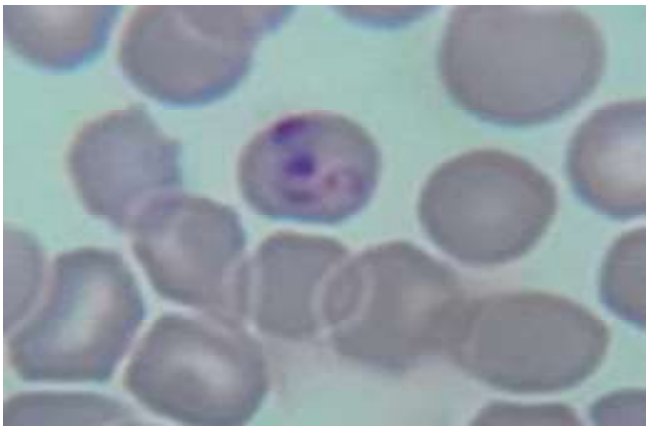

Fig. 2: Intraerythrocytic *Babesia gibsoni* organism (Arrow pointed)

b.wt., orally, bid) and Pantoprazole tablet (Pantop 40®, Aristo pharma, once daily) for six weeks. Further, the owner was advised to visit the VCC on the 7th, 14th, 30th, 50th, 90th, 180th, and 365th days to check for disease improvement or relapse.

Follow up

The dog's condition improved significantly with no clinical manifestations within the first week of treatment. On the 7th day complete blood count revealed improvement in Hb: 9.9 g/dl and WBC: 12.8 x $10^3/\mu l$, the blood smear was negative for protozoa. On 14th, 30th, 50th, 90th, 180th, and 365thdays, Hb and WBC counts were within the reference range, and blood smears were negative for hemoprotozoa. On the 30thday, ultrasonography revealed healthy spleen. Treatment was discontinued after six weeks. One and a half years have passed, and the dog is reported to be healthy, with no relapse of babesiosis.

Summary and Discussion

Conventional therapies for canine babesiosis include diminazene aceturate and imidocarb dipropionate, antiprotozoals (*e.g*., atovaquone), and antibiotics (clindamycin and azithromycin). Although the large-form canine *Babesia* species are sensitive to imidocarb dipropionate and diminazene aceturate, none of these drugs can completely eliminate the small form of *B. gibsoni* (Jefferies *et al*., 2017) and such patients become chronic carriers with frequent relapse of the condition following treatment (Bandula Kumara, 2016).Similarly, in the present case, the patient showed temporary recovery after treatment once with diminazeneaceturate and on second occasion with diminazine aceturate along with clindamycin. In addition to the problem of relapse, conventional treatment with babesiacidal drugs can lead to severe adverse side effects, for example, imidocarb causes severe inflammation, while diminazene aceturate leads to neurological symptoms (Abdullah *et al*., 1984; Hwang *et al*., 2000; Miller *et al*., 2005). The present refractory *Babesia gibsoni*infection has been successfully treated with a combination of clindamycin, doxycycline, and metronidazole. In a study to find a possible treatment strategy against canine *Babesia gibsoni* infection, a similar combination of drugs was reported to eliminate the infection in four dogs (Suzuki *et al*., 2007). Our findings contrast those showing a relapse of *Babesia gibsoni*infection in a dog after a similar combined treatment who recovered after a second continuous similar treatment (An *et al*., 2019). We could not explain the exact reason for this difference. Another problem with this treatment protocol is its longer duration. Our finding is based on clinical improvement. In similar line *B. gibsoni* was successfully treated in a dog with same treatment and two instances of the similar duration of treatment (An *et al*., 2019). Safety margin and mechanism of action need to be explained from the perspective of parasitology, immunology, and pharmacology in future studies.

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